8. CANCER DOSE-RESPONSE EVALUATION

8.1. INTRODUCTION

This chapter discusses the dose-response aspects of the key carcinogenicity data. The identification of a dose-response can enhance the understanding of the cancer hazard and lead to an estimation of possible disease impact. One measure of impact used by EPA is the cancer unit risk. Unit risk is the estimated cancer risk at 1 $\mu g/m^3$ of exposure, in this case $\mu g/m^3$ of diesel exhaust (DE) particulate matter, from a continuous 70-year exposure. Unit risk derivation procedures and specifications are defined in EPA's risk assessment guidance (U.S. EPA, 1986, 1996).

Evidence shows that DE is likely to pose a human hazard for lung cancer by the inhalation route of exposure. The mode of action (MoA) for humans has not been determined, and the presumed MoA for rats does not justify using these data to estimate cancer unit risk for humans. EPA believes that a role for both mutagenic effects and particle-specific effects is plausible. According to EPA Cancer Guidelines, the mutagenic effects would allow the modeling of dose-response using models with a linear term at low doses. With toxicologically suspect organics thought to be in proportion to the mass of particulates, the use of $\mu g/m^3$ of DE particles as the dosimeter is feasible. With no clear indication that key organic components have changed disproportionately to the particle mass over the years (note that the overall particle mass has been decreasing), the use of older toxicological results based on older engine exposures to predict current-day hazards is also feasible, though uncertainty exists in this assumption. The overall challenge with DE is to judge the uncertainties going into the dose-response analysis and decide whether to proceed and, if so, what certainties/uncertainties to ascribe to any resulting analysis and follow-on unit risk derivation. For DE, the cascade of desirable to less desirable approaches clearly starts with human data, then to comparative potency approaches that use various surrogate exposure-response relationships.

For a variety of reasons EPA is not, at this time, adopting or recommending a cancer unit risk or risk range for DE. EPA will monitor ongoing research and reanalysis of epidemiology-exposure studies and may revisit dose-response and unit risk derivation.

8.2. REVIEW OF PREVIOUS QUANTITATIVE RISK ESTIMATES

Early attempts to quantitatively assess the carcinogenicity of diesel engine emissions were hindered by a lack of positive epidemiologic studies and long-term animal studies. One means of overcoming these obstacles was the use of the so-called comparative potency method (Albert et al., 1983). An attempt to estimate risk based on human data was also made at this time by Harris (1983), although it was based upon equivocal evidence. By the late 1980s the availability of data

from animal bioassays and epidemiologic studies provided an opportunity to the derivation of both animal and human data-based estimates. See Table 8-1 for a historical overview.

8.2.1. Comparative Potency Method

In the comparative potency method, a combustion or pyrolysis product is selected that has a previously determined cancer potency estimate based on epidemiologic data. The ratios of the potency of this agent (e.g., coke oven emissions) to diesel particulate matter (DPM) extract in a variety of in vivo and in vitro tests are then multiplied by the epidemiology-based potency estimate for coke oven emissions and averaged. If epidemiology-based estimates from more than one pollutant are used, the derived potencies are generally averaged to obtain an overall mean.

The comparative potency estimate of Albert et al. (1983) is probably the best known. Their results were obtained using epidemiology-based unit cancer risk estimates for coke oven emissions, cigarette smoke condensate, and roofing tar. Samples of particulate matter were collected from three light-duty engines (a Nissan 220 C, an Oldsmobile 350, and a Volkswagen turbocharged Rabbit), all run on a highway fuel economy test cycle, and from a heavy-duty engine (Caterpillar 3304) run under steady-state, low-load conditions. The particulate matter was extracted with dichloromethane and tested in a variety of assays. Dose-dependent increases in response were obtained for the four assays listed below:

- Ames *Salmonella typhimurium* (TA98) reverse mutation,
- Gene mutation in L5178Y mouse lymphoma cells,
- Sencar mouse skin tumor initiation test, and
- Viral enhancement of chemical transformation in Syrian hamster embryo cells.

Only the first three assays were used to develop comparative potency estimates because of variability of responses in the enhancement of the viral transformation assay. The in vitro studies were carried out both in the presence and absence of metabolic activators. The potency, defined as the slope of the dose-response curve, was measured for each sample in each short-term assay.

The skin tumor initiation test was positive for all the engines tested except the Caterpillar engine. Only the Nissan engine, however, gave strong dose-response data. Because skin tumor initiation was considered to be the most biologically relevant test, it was used to derive potency estimates for the Nissan engine. An estimate for the Nissan engine was then derived by multiplying the epidemiology-based potency estimates for each of the three agents (coke oven emissions, roofing tar, and cigarette smoke condensate) by the ratios of their potencies in the skin tumor initiation test to that of the Nissan diesel engine. According to this method, three 95% upper-bound estimates of lifetime cancer risk per microgram per cubic meter of extractable

Table 8-1. Estimated 95% upper confidence limits of the lifetime risk of cancer from inhalation of 1 μg/m^3 diesel particulate matter (DPM)

Method	Potency	Comments	Reference
Comparative potency	3.5×10^{-5}	Nissan engine	Albert et al., 1983
Comparative potency	2.6×10^{-5}	Average of 3 engines	Albert et al., 1983
Comparative potency	7.0×10^{-5}	Light-duty engines	Cuddihy et al., 1984
Comparative potency	6.8×10^{-4}	Average of 3 engines	Harris, 1983
Multistage model	1.6×10^{-5}	Lung cancer rats[a]	Albert and Chen, 1986
Straight-line extrapolation	$6\text{-}12 \times 10^{-5}$	Lung cancer rats[b]	Pott and Heinrich, 1987
Time-to-tumor model	$2\text{-}3 \times 10^{-5}$	Lung cancer rats[a]	Smith and Stayner, 1990
Logistic regression	8×10^{-5}	Lung cancer rats[c]	McClellan et al., 1989
Multistage model	1.4×10^{-5}	Lung cancer rats[d]	Pepelko and Chen, 1993
Armitage-Doll model	5.2×10^{-5}	Lung cancer rats[a,e]	Hattis and Silver, 1994
Multistage model	8.9×10^{-5}	Lung cancer rats[f]	CAL-EPA, 1998
Multistage model	3.4×10^{-5}	Lung cancer rats[d]	WHO, 1996
Biological model	1.7×10^{-5}	Lung cancer rats[d]	Chen and Oberdorster, 1996
Biological model	3.5×10^{-6}	Assuming particle threshold	Chen and Oberdorster, 1996
Epidemiologic analysis	1.4×10^{-3}	London transport study	Harris, 1983
Epidemiologic analysis	6×10^{-4}	Railroad workers	CAL-EPA, 1998
Epidemiologic analysis	$0.6\text{-}2 \times 10^{-3}$	Railroad workers	U.S. EPA, 1998
Epidemiologic analysis	1.6×10^{-2}	Truck drivers[g]	Steenland et al., 1998

[a]Used data from studies by Mauderly et al., 1987.
[b]Used data from studies by Brightwell et al., 1989; Heinrich et al., 1986a; and Mauderly et al., 1987.
[c]Used data from studies by Brightwell et al., 1989; Ishinishi et al., 1986; Iwai et al., 1986; and Mauderly et al., 1987.
[d]Used data from studies by Brightwell et al., 1989; Ishinishi et al., 1986; and Mauderly et al., 1987.
[e]Maximum likelihood estimate based on 53 years of exposure, 8 hours/day, 240 days/year.
[f]Used data from studies by Brightwell, et al., 1989; Heinrich et al., 1995; Ishinishi et al., 1986; Mauderly, 1987; and Nikula et al., 1995.
[g]Estimated risk of 45 years occupational exposure to 5 μg/m^3.

organic matter were derived for the Nissan diesel, based on potency comparisons with each of the three agents. These values are: coke oven emissions, 2.6×10^{-4}; roofing tar, 5.2×10^{-4}; and cigarette smoke condensate, 5.4×10^{-4}. The average of the three equals 4.4×10^{-4}.

The potency of the other diesel emission samples was not estimated directly because of the weak response in the skin tumor initiation test. Instead, their potency relative to the Nissan engine was estimated as the arithmetic mean of their potency relative to the Nissan in the Salmonella assay in strain TA98, the sister chromatid exchange assay in Chinese hamster ovary cells, and the mutation assay in mouse lymphoma cells. The estimated lifetime cancer risk per microgram per cubic meter of extractable organic matter for extracts from these engines are as follows: Volkswagen, 1.3×10^{-4}; Oldsmobile, 1.2×10^{-4}; and Caterpillar, 6.6×10^{-6}.

To convert these values to a lifetime risk per microgram per cubic meter of total DPM, the results were multiplied by the fraction of extractable organic matter in the particles. This conversion was based on the assumption that the carcinogenic effects were caused solely by the organic fraction. These fractions were as follows: Nissan, 0.08; Volkswagen, 0.18; Oldsmobile, 0.17; and Caterpillar, 0.27. After this adjustment, the resulting estimated potencies per microgram per cubic meter of inhaled DPM varied from 3.5×10^{-5} for the Nissan to 1.8×10^{-6} for the Caterpillar.

Harris (1983) developed comparative potency estimates for the same four engines used by Albert et al. (1983) but used only two epidemiology-based potency estimates: those for coke oven emissions and for roofing tar. He employed preliminary data from three of the same assays used by Albert et al. (1983): the Sencar mouse skin tumor initiation assay, enhancement of viral transformation in Syrian hamster embryo cells, and the L5178 mouse lymphoma test. The mouse lymphoma test was used both with and without metabolic activation, whereas the Salmonella assay was not used.

The diesel cancer potency estimates by Harris (1983) were then derived by multiplying the epidemiology-based cancer potency estimates for both coke oven emissions and roofing tar by the ratio of their potencies compared with DE particles in each of the four bioassays. For example, the epidemiology-based relative risk of exposure to 1 $\mu g/m^3$ of coke oven emissions was estimated to equal 4.4×10^{-4}. In the skin tumor initiation test, 2.1 papillomas per mouse were reported for the coke oven sample, compared with 0.53 for the Nissan engine extract. The benzene-extractable fraction was assumed to equal 0.06 (slightly less than that in the Albert et al. [1983] studies). The diesel potency estimate using this comparison is then equal to $(0.53/2.1) \times 0.06 \times 4.4 \times 10^{-4}/\mu g/m^3$, or $6.6 \times 10^{-6}/\mu g/m^3$ DPM. A total of eight comparisons were made for each engine, four bioassays times two epidemiology-based potency estimates.

The Harris (1983) estimates are not comparable to those of Albert et al. (1983) without adjustment. The unit risk estimates of Albert and co-workers are based on absolute risk during

lifetime exposure, whereas Harris reported his values in terms of relative risk per year of exposure. To adjust this to lifetime risk for continuous exposure, it is necessary to multiply Harris' values by a factor of 2.7 = (70 × 0.039), where 70 reflects the lifetime exposure (70 years) and 0.039 is the lifetime lung cancer mortality rate in the U.S. population.

The range of potencies varied from 0.2×10^{-5} to 0.6×10^{-5} for the Nissan sample, 0.1×10^{-5} to 2.4×10^{-5} for the Oldsmobile 350, 0.2×10^{-5} to 27.8×10^{-5} for the Volkswagen Rabbit, and 0.1×10^{-5} to $2.5 \times 10^{-5}/\mu g/m^3$ DPM for the Caterpillar sample. Harris (1983) derived an overall mean relative risk value of $3.5 \times 10^{-5}/\mu g/m^3$ for the three light-duty engines with a 95% upper confidence limit of 2.5×10^{-4}. Individual mean values for each engine were not reported. After multiplying by 2.7 to convert to a unit risk, the upper-bound estimate of potency from the three light-duty engines was equal to $6.8 \times 10^{-4}/\mu g/m^3$ DPM. McClellan (1986), Cuddihy et al. (1981, 1984), and Cuddihy and McClellan (1983) estimated a risk of about $7.0 \times 10^{-5}/\mu g/m^3$ DPM using a comparative potency method similar to those reported in the preceding paragraph. The database was similar to that used by Albert et al. (1983) and Harris (1983). This estimate agrees quite well with those reported by Albert et al. (1983). Although the Harris (1983) estimate is somewhat greater, it should be remembered that it was based on preliminary data.

8.2.2. Suitability of Comparative Potency Approach

As noted earlier, in this method the potency of DPM extract is compared with other combustion or pyrolysis products, for which epidemiology-based unit risk estimates have been developed. Comparisons are made using short-term tests such as skin painting, mutations, and mammalian cell transformation. The ratio of the potency of DPM extracts to each of these agents is then multiplied by their unit risk estimates to obtain the unit risk for DE.

Although this test was based originally on the belief that cancer induction at low doses is due to the organic fraction present on the diesel particles, it is possible to argue, through a biologically based dose-response modeling concept, that the relative cancer risk of two compounds is approximately equal to the ratio of initiation rate of the two compounds at low doses even though particles may assert other effects at higher doses; thus, making it a reasonable approach for risk derivation. A major strength of this approach is avoidance of lung particle overload effects. Furthermore, independent tests have shown that the organic fraction of DE may damage DNA and thus may induce cancer (see Chapter 7). Finally, the carcinogenic potency of the organic fraction can be compared with related emissions for which cancer potency is reasonably well defined.

A major uncertainty of this approach is the assumption that cancer potency can be determined on the basis of the effectiveness of the organic fraction alone. Under lung particle overload conditions, particles are considered to play a primary role in lung cancer induction. As

noted in Chapter 4, ultrafine diesel particles may be ingested by epithelial cells even at low concentrations, inducing damage to the genetic material and possible carcinogenic effects. The potency estimates using this approach may therefore underestimate risk by not accounting for possible effects of particles or even reactive oxygen species. Association of organics with particles may also influence their potency depending on relative elution rates, efficiency of activation, etc. A final uncertainty involves the assumption that potency in short-term tests is an accurate predictor of lung cancer potency.

The uncertainties of this approach preclude its unilateral adoption for predicting upper-bound estimates.

8.2.3. Animal Bioassay-Based Cancer Potency Estimates

With the availability of chronic cancer bioassays, a considerable number of potency estimates were derived using lung tumor induction in rats. Albert and Chen (1986) reported a risk estimate based on the chronic rat bioassay conducted by Mauderly et al. (1987). Using a multistage model and assuming equivalent deposition efficiency in humans and rats, they derived a 95% upper confidence limit of 1.6×10^{-5} for lifetime risk of exposure to 1 $\mu g/m^3$. Pott and Heinrich (1987) used a linear extrapolation for data reported by Brightwell et al. (1989), Heinrich et al. (1986a), and Mauderly et al. (1987). They reported risk estimates of 6×10^{-5} to $12 \times 10^{-5}/\mu g/m^3$. More recently, Smith and Stayner (1990), using time-to-tumor models based on the data of Mauderly et al. (1987), derived 95% upper confidence limits ranging from 1.5×10^{-5} to $3 \times 10^{-5}/\mu g/m^3$. Pepelko and Chen (1993) developed unit risk estimates based on the data of Brightwell et al. (1989), Ishinishi et al. (1986), and Mauderly et al. (1987) using a detailed dosimetry model to extrapolate dose to humans and a linearized multistage (LMS) model. Taking the geometric mean of individual estimates from the three bioassays, they derived unit risk estimates of $1.4 \times 10^{-5}/\mu g/m^3$ when dose was based on carbon particulate matter per unit lung surface area rather than whole DPM, and $1.2 \times 10^{-4}/\mu g/m^3$ when based on lung burden per unit body weight. Hattis and Silver (1994) derived a maximum likelihood estimate for occupational exposure of $5.2 \times 10^{-5}/\mu g/m^3$ based on lung burden and bioassay data reported by Mauderly et al. (1987) and use of a five-stage Armitage-Doll low-dose extrapolation model. The EPA (1998) derived a unit risk estimate of $3.4 \times 10^{-5}/\mu g/m^3$, based on lung burden of DPM per unit lung surface area, using an LMS model and calculating the geometric mean from results of bioassay data reported by Mauderly et al. (1987), Ishinishi et al. (1986), and Brightwell et al. (1989). California EPA (OEHHA, 1998) derived a geometric mean estimate of $6 \times 10^{-5}/\mu g/m^3$ from five bioassays using an LMS model.

In an attempt to demonstrate the possible influence of particle effects as well as particle-associated organics, an additional modeling approach was attempted by Chen and Oberdorster

(1996). Employing a biologically based two-stage model and using malignant tumor data from Mauderly et al. (1997), the upper bound risk estimate for exposure to 1 $\mu g/m^3$ was estimated to be 1.7×10^{-5}. This estimate is virtually identical to that using the LMS model, assuming nonthreshold effect of particles. If a threshold of particle effect is assumed, however, the estimated risk decreases about fivefold. The results also show that the mechanism of diesel-induced lung tumor at high exposure concentrations may differ from that at low exposure concentrations, with organics and particles playing primary roles of tumorigenesis respectively at low and high concentrations.

8.2.4. Suitability of Laboratory Animal Bioassay Approach

Cancer risk assessment from exposure to DE, based on available animal bioassays, traditionally has strengths and uncertainties. For DE the best studies are adequately designed, eliminating confounding factors often present in epidemiology studies. Exposure duration and exposure levels can be precisely controlled and monitored. The presence or absence of tumors can be verified by pathological evaluation. Although animal-to-human extrapolation of dose is required and has uncertainty, the development of dosimetry models has eliminated much of the uncertainty in this area. Nevertheless, two important uncertainties remain: the adequacy of the rat as a model for evaluating human risk of cancer from exposure to DE and the shape of the dose-response curve.

It is believed by a consensus of experts that the rat seems to be unique in its response to particulate matter, and therefore its use for assessing human lung cancer risk is problematic (ILSI, 1998; Mauderly, 1994). As noted in Chapter 7, the rat is the only species that has unequivocally been shown to develop lung cancer in response to inhaled DE. However, what is happening in the human lung is uncertain. It has also been argued that humans are more resistant to particle-induced lung cancer; although coal miners develop pneumoconiosis, lung cancer seldom occurs. Rats, on the other hand, were reported to develop lung cancer in response to coal dust (Martin et al., 1977), though this study was poorly described and the number of animals exposed was small (4/36 developed lung cancer). Moreover, exposure levels were very high and lung burdens were greater than those generally encountered in coal miners (Mauderly, 1994). Although lung cancer has not been reported in most epidemiology studies of coal miners, Zhong and Dehong (1995) reported that Chinese workers suffering coal miners' pneumoconiosis did have an increased risk of lung cancer.

Although rat data may still have limited value for hazard identification they are much less suitable for quantitating human environmental risk. For example, particle deposition patterns are different in the rat and human. Because of the absence of respiratory bronchioles in the rat, a greater fraction of inhaled particles deposit in the alveolar regions; in primates, deposition occurs

to a larger extent at the bifurcation of the small bronchi. Differing deposition patterns are likely to result in different pathologic responses, as reported by Nikula et al. (1997) for rats and monkeys.

Another major uncertainty in the use of rat bioassay data concerns extrapolation of lung cancer to ambient concentrations. Significant lung tumor increases in experimental animals have generally been obtained only at concentrations resulting in lung particle overload with concomitant pathological effects. As discussed in Section 7.4, it has been hypothesized that lung cancer induction results from a secondary effect associated with release of various inflammatory mediators by particle-overloaded phagocytic cells. The resultant inflammatory response, with accompanying cell division, can increase the likelihood that any oxidant-induced or spontaneously occurring genetic damage becomes fixed in a dividing cell and is clonally expanded (Driscoll, 1995).

If the primary means of lung cancer induction in rats is via particle-overload mechanisms, then it can be surmised that different factors are plausibly responsible for induction of lung cancer in humans exposed at occupational or ambient concentrations. Experimental evidence provides some support for the existence of low-dose mechanisms. Riebe-Imre et al. (1994) reported that carbon black is taken up by lung epithelial cells in vitro, inducing chromosomal damage and disruption of the cytoskeleton (lesions that closely resemble those in tumor cells) at concentrations that did not induce measurable toxicity. Ichinose (1997a, b) reported that not only are reactive oxygen species generated from organics present on the surface of diesel particles, but the production of these radicals is well correlated with increased in 8-hydroxydeoxyguanine adducts. Finally, Dasenbrock et al. (1996) reported that extraction of the organic fraction from diesel particles decreased their carcinogenic potency, suggesting a role for organic constituents. Because the primary modes of cancer induction are likely to differ as exposure concentrations decrease below those required to induce lung particle overload, the slope of the dose-response curve is also likely to change. Since a change in slope at low doses cannot be determined from available bioassay data, low-dose extrapolation results in a considerable degree of uncertainty.

In summary, the use of rat data to quantitate human cancer risk at environmental exposures is not recommended.

8.2.5. Epidemiology-Based Estimation of Cancer Potency

The first lung cancer risk estimates based on epidemiologic data were derived by Harris (1983). He assessed the risk of exposure to diesel engine emissions using data from the London Transport Worker Study reported by Waller (1981). Five groups of employees from the London Transport Authority (LTA) were used: bus garage engineers, bus drivers, bus conductors, engineers in central works, and motormen and guards. The first group was considered to have

received the highest exposure; the next two, intermediate; and the last two, none. When cancer death rates for the high-exposure group were compared with those of London males, there was no increase in the observed-to-expected (O/E) ratios. The author, in fact, considered the results to be negative. However, because the low rate of lung cancer in all the LTA exposure groups may have been the result of a "healthy worker" effect, Harris (1983) compared the exposed groups with internal controls. He merged the three exposed groups and compared them with the two groups considered to be unexposed. An adjustment was made for the estimated greater exposure levels of garage engineers compared with bus drivers and conductors. Using this method, the relative risk of the exposed groups was greater than 1 but was statistically significant only for garage engineers exposed from 1950 to 1960. In this case, the O/E ratio was 29% greater than the presumed unexposed controls.

Harris (1983) identified a variety of uncertainties relative to potency assessment based on this study. These included:

- Small unobserved differences in smoking incidences among groups, which could have a significant effect on lung cancer rates;
- Uncertainty about the magnitude of exposure in the exposed groups;
- Uncertainty regarding the extent of change in exposure conditions over time;
- Random effects arising from the stochastic nature of the cancer incidence; and
- Uncertainty in the mathematical specification of the model.

Taking the uncertainties into account, he derived a maximum likelihood excess relative risk estimate of 1.23×10^{-4} with a 95% upper confidence limit of $5 \times 10^{-4}/\mu g/m^3$ DPM per year. These estimates are equal to 5×10^{-4} and 2×10^{-3}, respectively, when converted to an absolute risk for lifetime exposure to 1 $\mu g/m^3$ particulate matter. It should be noted that, because of the high degree of uncertainty, the 95% lower confidence limit would predict no risk.

McClellan et al. (1989) reported risk estimates based on the Garshick et al. (1987) case-control study in which lung cancer in railroad workers was evaluated. Using a logistic regression, the expected relative risk of lung cancer death was estimated to rise 0.016 per year of exposure to DE. Adjustments were made to convert to continuous exposure (168 vs. 40 hours) for 70 years. Because exposure levels could not be defined exactly, two sets of calculations were made, assuming inhaled DPM concentrations of either 500 or 125 $\mu g/m^3$ DPM. Using a 95% upper confidence limit, the number of excess cancer deaths per year in the United States was estimated to range from 1900 to 7400. Employing these values, the lifetime 95% upper confidence limits of the risk from exposure to 1 $\mu g/m^3$ DE can be derived, by dividing the estimated excess number of annual cancer deaths in the United States by the total population and multiplying by 70, the estimated mean lifespan. Based upon the exposure estimates of 500 or 125 $\mu g/m^3$ DPM, unit risks

of 0.6×10^{-3} and $2 \times 10^{-3}/\mu g/m^3$ were derived. Even using the 95% lower confidence limits, an excess of 100 to 400 deaths is predicted, unlike the Harris (1983) study in which no excess deaths could be predicted based on the lower confidence limit.

California EPA (1998) derived unit risk estimates for lung cancer, based upon the Garshick et al. (1987) case-control study and the Garshick et al. (1988) cohort study of U.S. railroad workers. A variety of exposure patterns were considered, characterized by two components: the average exposure concentration for the workers as measured by Woskie et al. (1988) and the extent of change from 1959 to1980. The lowest lifetime risk estimate derived was $1.3 \times 10^{-4}/\mu g/m^3$ and the highest was $2.4 \times 10^{-3}/\mu g/m^3$. The geometric mean was $6 \times 10^{-4}/\mu g/m^3$.

Steenland et al. (1998) estimated lung cancer risk of truck drivers on the basis of a case-control study of decedents in the Teamsters Union (Steenland et al., 1990). Retrospective exposure estimates were made starting with a set of 1991 exposure measurements for different job categories and then retrospectively estimating from 1982 to about 1950 using various factors, including diesel vehicle miles traveled and DE engine emission rates per mile. The 1991 job category estimates came from an extensive industrial hygiene survey of elemental carbon (EC) exposures in the trucking industry by Zaebst et al. (1991). Lifetime (through age 75) excess risk of lung cancer death for male truck drivers was calculated with the aid of a cumulative exposure model. Assuming a most likely emissions scenario of 4.5 gm/mile in 1970, and a 45-year exposure to 5 $\mu g/m^3$ of EC beginning at age 20 and ending at age 65, the estimated excess lung cancer risk was determined to be 1.6% (95% CI 0.4%-3.1%).

8.2.6. Suitability of Using Epidemiologic Data

A major advantage in the use of human data is the elimination of uncertainty due to possible differences in sensitivity to cancer induction by DE among species. Second, epidemiology studies are based on occupational exposures, which generally occur at concentrations insufficient to result in lung particle overload. Thus, lung cancer in the human studies is likely to be induced by non-particle-overload mechanisms (at least as defined in the rat studies) under either occupational or ambient exposure levels. Uncertainty in extrapolating risk from occupational studies is therefore decreased, not only because low-dose extrapolation occurs over a smaller range, but because mechanisms of cancer induction are less likely to vary within this range with accompanying changes in the dose-response curve.

There is considerable evidence for nonoverload mechanisms of cancer induction by products of fossil fuel combustion. Mumford et al. (1989) reported greatly increased lung cancer concentration of PAHs but lacks an insoluble carbon core. Increased levels of aromatic DNA mortality in Chinese communes burning so-called smoky coal containing high concentrations of polycyclic aromatic hydrocarbons (PAHs). Demonstration of the carcinogenicity of coke oven

emissions in humans (Lloyd, 1971) also provided evidence for a role by organics because coke oven PM contains a high adducts were reported in bus maintenance and terminal workers by Hemminki et al. (1994) and in garage workers and mechanics exposed to DE (Nielsen and Autrup, 1994). Studies by Sagai et al. (1993) have indicated that DPM could produce superoxide and hydroxyl radicals in vitro without any biologically activating systems. On the basis of these findings, they suggested that most DE toxicity in lungs is due to active oxygen radicals. In a more recent study, these investigators reported that instillation of only 0.1 mg of DPM into mouse lungs resulted in the production of 8-hydroxyguanosine in lung cell DNA. The critical lesion may thus be induced by oxygen free-radicals generated from DPM (Nagashima et al., 1995).

An uncertainty associated with most of the diesel epidemiology studies was the inability to eliminate all confounding factors, resulting in possible errors in estimating relative risk ratios. Small errors in adjustment for smoking, for example, can result in considerable error because smoking has a much larger effect on relative cancer risk than is likely for DE. The likelihood of significant confounding errors in the Garshick et al. (1987, 1988) studies is decreased by the considerable effort exerted to eliminate or reduce such factors, especially smoking. Moreover, meta-analyses by Bhatia et al. (1998) and Lipsett et al. (1999) using a number of diesel epidemiology studies resulted in relative risk ratios quite similar to the one reported by Garshick et al. (1987). Although exposure levels are likely to have differed somewhat among studies, the agreement still suggests that a relative risk near 1.4 is a reasonable approximation.

The greatest uncertainty in estimating DE-induced cancer risk from epidemiology studies is determination of exposure levels. Even though DPM concentrations were often measured near the end of the studies, historic exposure data are generally lacking. Such information is critical, since there is indirect evidence, based on other pollutant measurements such as nitrogen oxides, that exposure levels have decreased considerably in recent years, especially in the railroad industry (Woskie et al., 1988a). In the only historic study found in which DPM was measured, Heino et al. (1978) reported average concentrations of 2 mg/m^3 in Finnish roundhouses. Woskie et al. (1988b), by contrast, reported a mean of 134 $\mu g/m^3$ for roundhouse workers near the end of the Garshick et al. (1987, 1988) studies. While the relationship between DPM concentrations in Finnish and U.S. railroad roundhouses during the 1970s is uncertain, it does point to the likelihood that exposure levels have decreased over time.

With some of the uncertainties about the dose-response for both railroad workers and truck drivers being actively investigated by EPA, NIOSH, and others, EPA feels that additional in-depth dose-response analysis should await the newer data that are expected during 2000.

8.2.6.1. *Railroad Worker Data*

Although there have been previous efforts to use Garshick's cohort data to conduct a quantitative risk assessment, a consistent dose-response between DE exposure and lung cancer has not been found. Both positive and negative dose-responses have been reported, depending on how the data are analyzed. These conflicting analyses have become a source of continuing debate about estimated cancer risk to humans through DE exposure. Presently, a known mortality under count in the Garshick data is being funded by NIOSH and updated by Garshick. In the near future this updating will likely be reanalyzed by several risk assessing institutions to see if some of the uncertainties have been resolved. For these reasons, EPA will not conduct its own quantitative risk assessment until more information becomes available. This decision should not be construed to imply that the railroad worker studies contain no useful information on lung cancer risk from exposure to DE.

Crump et al. (1991) reported that the relative risk can be positively or negatively related to the duration of exposure depending on how age was controlled in a model. Garshick et al., (1988) reported a positive relationship of relative risk and duration of exposure by modeling age in 1959 as a covariant in an exposure-response model. The positive relationship disappeared when attained age was used instead of age in 1959. This negative dose-response continues to be upheld and further clarified in Crump (1999). California EPA (Cal-EPA, 1998) also found a positive dose-response by using age in 1959 but allowing for an interaction term of age and calendar year in the model. Cal-EPA produced a unit risk estimate in the range of 10^{-3} to 10^{-4}.

A recent special report by HEI (1999) also suggested there was no positive dose-response if a model similar to that used by Cal-EPA included a variable to stratify data into three job categories: clerks, shop workers, and train workers. This observation suggests that one should be cautious in estimating relative risk by taking the ratio of two relative risks calculated from two different job groups (e.g., train workers vs. clerks) because there appear to be some unknown job-category-specific effects operating among these groups.

8.2.6.2. *Teamster Truck Driver Data*

Steenland et al. (1998) is a case-control study of members of the Teamsters Union who died in 1982-1983. Smoking histories were obtained from next of kin. Available data indicate that exposure to workers in the trucking industry in 1990 averaged 2-27 $\mu g/m^3$ of elemental carbon (EC). The exposure information in 1990 was used as a baseline exposure measurement to reconstruct past exposure (in the period of 1949 to 1983) by assuming that the exposure for workers in different job categories is a function of highway mileages traveled by heavy-duty vehicles, and efficiency of the engine over the years.

Steenland et al. (1998) provide a potentially valuable database for calculating unit risk for DE emissions. The strength of this data set is that the smoking history of workers were obtained to the extent possible. Smoking is especially important in assessing the lung cancer risk due to DE exposure, because smoking has much higher relative risk (or odds ratio) of lung cancer in comparison to that of DEP. For the Steenland et al. (1998) study, the overall (ever-smokers vs. nonsmokers) odds ratio for smoking is about 7.2, which is about fivefold larger than the 1.4 odds ratio of diesel exposure. It is possible that a moderate change of information on smoking and diesel exposure might alter the conclusion and risk estimate.

EPA has noted that Steenland's Teamsters Union truck driver case control study workers had cumulative exposure ranging from 19 to 2440, with the median and 95th percentile respectively of 358 and 754 μg/m^3-years of EC. These EC levels correspond respectively to 197 and 415 μg/m^3-years of DE in ambient air, or approximately 3 and 6 μg/m^3 of DE in ambient air. This information is useful for comparing the exposure of the trucking personnel to animal bioassay exposures and to estimated environmental exposures.

Steenland et al. (1998) indicate that their risk assessment is exploratory because it depends on estimates about unknown past exposures. With the Steenland risk assessment being a recent publication, independent evaluation of the uncertainties have been limited to HEI (1999) and a few interactions with stakeholders. HEI raised questions about the exposure estimates and the selection of controls; EPA has also noted that it may have databases to facilitate the development of improved exposure estimates. EPA and NIOSH are jointly pursuing some of the questions, including the exposure aspects. This work will be ongoing well into 2000.

Give the ongoing review and reanalysis, EPA will not use the Steenland occupational risk assessment to derive equivalent environmental parameters and cancer unit risk estimates until the additional investigation and reanalysis is completed and can be evaluated.

8.3. OBSERVATIONS ABOUT RISK

8.3.1. Perspectives

A decision has been made for this report that, despite the finding that DE is best characterized as highly likely to be a lung cancer hazard, the available data are currently unsuitable to make a confident, quantitative statement about the magnitude of the lung cancer risk attributable to DE at ambient exposure levels. However, the following information is provided to put DE cancer hazard in perspective and to help decision makers and the public make prudent public health judgments in the absence of a definitive estimate of the upper bound on cancer risk.

The characterization of lung cancer hazard is based on over 20 studies that demonstrate a consistent, positive association between exposure to DE in occupational settings and lung cancer risk. Several meta-analyses have also reported this consistent but relatively low increase in

relative risk of about 40%. Notwithstanding the discussion that was previously presented as to why these relative risk estimates and their attendant exposure assessments are uncertain, these positive associations suggest the potential for lung cancer risk at typical, historical occupational exposures. Since epidemiology is a relatively crude tool, we have come to expect that increased risks that are discernable over background cancer mortality in such studies will generally exceed 1 $\times 10^{-5}$ (1 in 100,000) and are often as high as 1×10^{-3} (1 in 1000). Unless the magnitude of the risk is in this range, given typical population sizes and competing biases that tend toward the null, results would be expected to be nonpositive (no statistically significant association). If actual risk were much higher than this ($>10^{-3}$ or 1 in 1000), relative risks would probably be much higher. While ambient average exposures are surely less than workplace exposures today, the margin of exposure for some individuals at the high end (>90 percentile) of the exposed population compared to the lower end of occupational exposures appears to be less than a factor of 10. This means that, when occupational exposures are converted to full day rather than workday and proximity to urban sources is considered, some individuals in the population may be experiencing exposures that are close to or even overlapping the exposures characterized in the Steenland et al. (1998) truckers study. Exposure estimates reported in that study are the focus of additional scrutiny but, based on EPA insights about the exposure review, it seems unlikely that exposure estimates would change by orders of magnitude and significantly alter the perspective just presented. While this perspective falls short of providing a definitive estimate of risk, it should be useful in providing a perspective on potential risk.

In addition, approaches to characterize risk to DE using comparative potency methodologies suggest that upper-bound risks under estimated ambient exposure situations could be in the range of 10^{-4} to 10^{-5} with upper-bound unit risk estimates clustering around 10^{-5} per $\mu g/m^3$ of DEP. While this approach is not amenable to deriving a reliable point estimate of upper-bound lung cancer risk for reasons described in Section 8.2., it does help to put potential risk in perspective because it relies on comparisons with other combustion products (coke oven emissions or cigarette smoke condensate) or from pyrolysis products (roofing tar) for which epidemiologic-based unit risk estimates have been developed.

EPA (1998) also developed a cancer risk estimate using benzo(a)pyrene (B[a]P) as a dosimeter. Pike and Henderson (1981) found good agreement when relating the concentration of (B[a]P) to lung cancer risk in smokers, British gas workers, U.S. coke oven workers, and U.S. hot pitch workers and when comparing residents of rural and urban locations. They concluded that while B[a]P is unlikely to be the only carcinogen and perhaps not even the most important one present in combustion emissions, nevertheless it serves as a reasonably accurate dosimeter. Based on an estimated cancer risk of 1/1500 per ng/m^3 B[a]P and a reported B[a]P concentration of 3.9 ng/µg DEP in exhaust from a Volkswagen engine (Heinrich et al., 1995), a maximum

likelihood estimate of cancer risk from lifetime exposure to 1 μg/m^3 can be calculated to be 3×10^{-6}. The 95% upper bound was not derived, but was estimated to be near 1×10^{-5}. The use of B(a)P as a dosimeter provided reasonably good estimates of lung cancer risk for combustion and pyrolysis products of coke ovens, hot pitch, gas production, refining, etc., in spite of the fact that B(*a*)P may constitute a relatively small fraction of the carcinogens present in these emissions. Risk estimates were based on well-documented lung cancer rates in the occupationally exposed groups. On the other hand, while predictions are good for the pollutants tested, the particles present from those combustion sources, unlike diesel particles, generally lack an insoluble carbon core. As noted in Chapters 3 and 7, adsorption to an insoluble particle core is likely to influence potency of individual organic components because of possible differing elution or activation rates. Estimates of cancer risk will also vary based on B(*a*)P concentration on the particle. The variability in B(*a*)P concentration among different DE sources and its effect on cancer potency have not been evaluated in detail. While this approach appears to be useful for estimating risk from a variety of related combustion emissions, because these emissions lacked an insoluble core, there is uncertainty.

In the absence of definitive risk estimates in this assessment, the three perspectives just discussed are not to be taken as absolutes, but rather as an outlook. With ongoing investigations regarding the existing key epidemiologic studies, as well as newly started epidemiologic studies focused on diesel exhaust, there are likely to be new future opportunities to consider risk estimation for diesel exhaust.

8.4. SUMMARY OF CANCER DOSE-RESPONSE CONSIDERATIONS

A number of attempts have been made to estimate cancer risk from exposure to DE. The present scientific consensus, however, suggests that animal- and other nonhuman-based risk estimates are too uncertain to extrapolate to humans. Therefore, EPA will focus on the use of epidemiological data to develop quantitative risk assessment. Because some of the uncertainties about the dose-response for both railroad workers and truck drivers can be reduced or better characterized by obtaining additional data within a reasonable time frame, EPA sees no value at this juncture in further teasing the existing data with additional dose-response analysis to unravel some of the uncertainties. With additional investigations underway in two of the richest epidemiology data sets, the railroad worker data base and the Teamster truck driver database, EPA will await developments before taking additional steps to derive a cancer unit risk for exposure to DE. EPA expects this newer information to be incrementally available throughout 2000.

At this time EPA is not adopting or recommending any cancer unit risk estimate for DE.

While there are uncertainties and controversy with the DE risk estimates that are available from various investigators, this uncertainty can not be resolved with currently available scientific information. The uncertainty about estimating unit cancer risk should not be confused with the inference that DE is "highly likely" to be a human carcinogen and that most would agree that it has produced risk (e.g., a relative risk increase of about 1.4) in some occupational settings. This elevation of risk is of public health concern even though the exposure-lung cancer risk relationship (e.g., unit risk) is uncertain. This concern is further demonstrated when comparing some high end environmental exposure estimates to lower end occupational exposure estimates and realizing that the exposure margin seems to be relatively small. Having information to put the DE cancer hazard into perspective may be useful in the absence of definite risk estimates.

Risk estimates derived from epidemiology studies are preferred for DE and are the pursuit of additional research and analysis.

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